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Signed Andrew Gersey

Dated 7 June 2005

Patents Form 1/77

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11 MAY 2004
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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

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1. Your reference — PH0423

11MAY04 E895006-1 D03022
P01/7700 0.00-0410448.5 ACCOUNT CHA

2. Patent application number
(The Patent Office will fill this part in) — 0410448.5

11 MAY 2004

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

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Patents ADP number *(if you know it)* 8866675001

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

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4. Title of the invention

PURIFICATION METHODS

5. Name of your agent *(if you have one)*

HAMMETT, Audrey, Grace, Campbell; ROLLINS, Anthony, John; HAMMER, Catriona, MacLeod and BRYAN, Ian, Bennett

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

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Patents ADP number *(if you know it)*

6. Priority: Complete this section if you are declaring priority from one or more earlier patent applications, filed in the last 12 months.

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. Divisionals, etc: Complete this section only if this application is a divisional application or resulted from an entitlement dispute (see note f)

Number of earlier UK application	Date of filing *(day / month / year)*

8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request?

Yes

Answer YES if:

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.

Otherwise answer NO (See note d)

9. Accompanying documents: A patent application must include a description of the invention. Not counting duplicates, please enter the number of pages of each item accompanying this form:

Continuation sheets of this form	
Description	15
Claim(s)	5
Abstract	0
Drawing(s)	0

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent (Patents Form 7/77)	
Request for a preliminary examination and search (Patents Form 9/77)	1
Request for a substantive examination (Patents Form 10/77)	
Any other documents (please specify)	

11. I/We request the grant of a patent on the basis of this application.

Signature(s) HAMMETT, Audrey, Grace, Campbell Date 10 May 2004

12. Name, daytime telephone number and e-mail address, if any, of person to contact in the United Kingdom

HAMMETT, Audrey, Grace, Campbell
01494 542747
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Notes

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f) Part 7 should only be completed when a divisional application is being made under section 15(4), or when an application is being made under section 8(3), 12(6) or 37(4) following an entitlement dispute. By completing part 7 you are requesting that this application takes the same filing date as an earlier UK application. If you want the new application to have the same priority date(s) as the earlier UK application, you should also complete part 6 with the priority details.

PURIFICATION METHODS

The present invention relates to novel processes for the purification of radiolabelled tracers, in particular for purification of ^{18}F- and ^{11}C-labelled compounds which may be suitable for use as Positron Emission Tomography (PET) radiotracers or for radio-iodinated compounds which may be suitable for use in PET or SPECT imaging.

Radiosynthesis of compounds of clinical interest often employs non-radioactive organic precursors in amounts which are in large excess relative to the amount of radiolabelling agent used. Excess precursors must be removed from the reaction mixture before the radiolabelled compound can be used clinically, this is conventionally done by a chromatographic procedure such as high performance liquid chromatography (HPLC). Given the limited half-life of most clinically useful radioisotopes, it is desirable to complete the radiosynthesis and purification as rapidly as possible. For example, ^{18}F has a half-life of 110 minutes and ^{18}F-labelled tracers for PET are therefore synthesised and purified within one hour of clinical use. Therefore, there exists a need for purification techniques which are rapid and efficient.

The present invention provides processes for separating radiolabelled compounds from their precursors rapidly and chemoselectively.

According to a general aspect of the invention, there is provided a process for purifying a radiolabelled product which comprises use of a solid-support bound scavenger group of formula (IV):

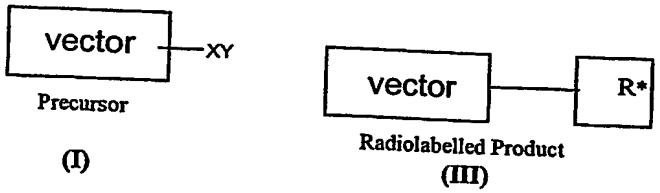
(IV)

wherein Z is a scavenger group and SP is a solid support.

In a further aspect of the invention, there is provided a process comprising the

steps of:

(a) contacting a solution-phase mixture of a radiolabelled product of formula (III) and excess precursor of formula (I):



wherein XY is a functional group and R* is a radioisotope or radiolabelled portion; with a compound of formula (IV):

(IV)

wherein Z is a scavenger group;

such that the compounds of formulae (IV) and (I) may form a covalent bond to each other;

(b) separation of purified radiolabelled product of formula (III) in the solution phase.

Suitably, the radiolabelled product of formula (III) contains an ^{18}F-label and is, for example 2-fluoro-2-deoxy-D-glucose ([^{18}F]-FDG), 6-fluoro-L-DOPA ([^{18}F]-FDOPA), 3'-deoxy-3'-fluorothymidine ([^{18}F]-FLT), 2-(1,1-dicyanopropen-2-yl)-6-(2-fluoroethyl)-methylamino)-naphthalene ([^{18}F]-FDDNP), 2-, 5-, and 6-fluoro (2(S)-azetinylmethoxy)pyridines, N-succinimidyl-4-[^{18}F]fluorobenzoate ([^{18}F]-SFB), an ^{18}F-labelled amino acid such as [^{18}F]-1-amino-3-fluorocyclobutane-1-carboxylic acid ([^{18}F]-FACBC), an [^{18}F]-labelled benzothiazole such as those described in international patent application WO 02/16333, [^{18}F]CFT, [^{18}F]FETNIM, [^{18}F]dopamine, an ^{18}F-labelled peptide for example somatostatin analogues, such as octreotide, bombesin, vasoactive intestinal peptide, chemotactic peptide analogues, α-melanocyte stimulating hormone, neurotensin, Arg-Gly-Asp peptide

and its analogues, human pro-insulin connecting peptide, endothelin, angiotensin and formyl-norleucyl-leucyl-phenylalanyl-norleucyl-tyrosyl-lysine, suitably Arg-Gly-Asp peptide and its analogues, such as those described in international patent applications WO 01/77415 and WO 03/006491, or a protected derivative of any thereof.

Alternatively, the radiolabelled product of formula (III) contains a ^{11}C-label and is, for example, [^{11}C]raclopride, [^{11}C-carboxyl]L-DOPA, [^{11}C-carboxyl]5-hydroxytryptophan, [^{11}C]-WAY-100635, [^{11}C]-deprenyl, [^{11}C]phenylephrine, [^{11}C]FLB457, [^{11}C]SCH23390, [^{11}C]SCH39166, [^{11}C]-NNC112, [^{11}C]NNC756, [^{11}C]MDL100907, [^{11}C]DSAB, [^{11}C]PK11195, [^{11}C]GR205171, [^{11}C]RTI-32, [^{11}C]CIT, [^{11}C]CFT, [^{11}C]flumazenil, [^{11}C]-diprenorphine, [^{11}C]-metomidate, [^{11}C]SCH442416, [^{11}C]carfentanil, or a ^{11}C-labelled benzothiazole such as those described in international patent application WO 02/16333, or a protected derivative of any thereof.

Alternatively, the radiolabelled product of formula (III) contains a radioiodine label, and is for example, 2-beta-carbomethoxy-3-beta-(4-iodophenyl)-8-(3-fluoropropyl)-nortropane or a protected derivative thereof.

The radiolabelled product of formula (III) comprises a vector portion being a molecular fragment having with an affinity for a given biological target (such as a modified drug pharmacaphore or peptide) and a radioisotope or radiolabelled portion represented by R*.

The precursor of formula (I) comprises the same vector portion as the radiolabelled product of formula (III) but bears a functional group –XY as described below.

Many radiosyntheses involve radioalkylation such as [^{11}C]alkylation, or radiohalogenation such as [^{18}F]fluorination or [^{18}F]fluoroalkylation, of precursors of formula (I). Treatment of the precursor with a radioisotope or radiolabelling agent

of formula (II) gives rise to a mixture containing the desired radiolabelled product of formula (III) and excess unreacted precursor of formula (I). The precursor of formula (I) therefore contains a functional group -XY which is capable of reacting with the radioisotope or radiolabelling agent of formula (II) shown in scheme I. The functional group -XY is suitably a leaving group such as a sulphonate ester preferably the mesyl, tosyl, nosyl or is a trimethylammonium salt or is a functional group which can react site-specifically with a moiety on the radiolabelling agent of formula (II) to form a stable covalent bond and is preferably chosen from the groups adehydes, ketones, aminooxy, hydrazides, hydrazines, alpha-haloacetyl or thiol.

In the compound of formula (IV), the scavenger group Z is suitably an isocyanate, isothiocyanate, thiol, hydrazine, hydrazide, aminooxy, aldehyde or ketone.

Scheme 1.

In the compounds of formulae (IV) and in the following more specific aspects of the invention, the "Linker" may be any suitable organic group which serves to space the scavenger group Z sufficiently from the solid support structure so as to maximise reactivity. Suitably, the Linker comprises zero to four aryl groups (suitably phenyl) and/ or a C_{1-6} alkyl or C_{1-6} haloalkyl (suitably C_{1-6} fluoroalkyl), and optionally one to four additional functional groups such as an amide or sulphonamide groups. In a preferred embodiment the linker is a polyethylene glycol containing moiety.

Compounds of formula (IV) may be prepared by methods known to the person skilled in the art, or are available commercially, for example from Novabiochem.

In a further aspect of the invention, there is provided a process comprising the steps of:

(a) contacting a solution-phase mixture of a radiolabelled product of formula (IIIa) and excess precursor of formula (Ia):

wherein R^1 is C_{1-6} alkyl and R* is [^{11}C]-C_{1-4}alkyl, such as -$^{11}CH_3$

with a compound of formula (IVa):

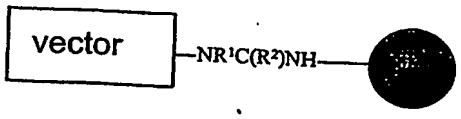
(IVa)

wherein R^2 is oxygen or sulphur

such that the compounds of formulae (IVa) and (Ia) may form a covalent bond to each other; and

(b) separation of purified radiolabelled product of formula (IIIa) in the solution phase.

The compounds of formula (IVa) and (Ia) react to form the corresponding urea or thiourea of formula (Va):



(Va)

wherein R^1 and R^2 are as defined for the compounds of formulae (Ia) and (IVa) respectively.

The purification process using a compound of formula (IVa) may be performed at a non-extreme temperature such as 10 to 120°C, suitably at ambient temperature to 80°C and using an inert solvent such as xylene, N,N-dimethylformamide (DMF) or chloroform.

In this aspect of the invention, the compound of formula (IIIa) is suitably a ^{11}C-labelled tertiary amine such as [^{11}C-CH_3]-2-Pyridin-4-yl-quinoline-8-carboxylic acid (2-dimethylamino-ethyl)-amide, [N-^{11}C-methyl]dimethylphenethylamine, or [^{11}C]DASB, and the precursor of formula (Ia) is the corresponding secondary amine such as 2-pyridin-4-yl-quinoline-8-carboxylic acid (2-methylamino-ethyl)-amide.

In a further aspect of the invention, there is provided a process comprising the steps of:

(a) contacting a solution-phase mixture of a radiolabelled product of formula (IIIb) and excess precursor of formula (Ib):

(Ib)

(IIIb)

wherein either

(i) the functional group $-X^bY^b$ in the compound of formula (Ib) is $-OSO_2R^3$ wherein R^3 is C_{1-15} alkyl or C_{1-10} alkylaryl and R^3 is optionally substituted by halo (preferably

fluoro), for example R^3 is methyl, para-toluene, trifluoromethyl, and R^{*b} in the compound of formula (IIIb) is a radiohalogen such as radiofluoro (for example ^{18}F) or radioiodo (such as ^{123}I, ^{124}I, or ^{125}I); or

(ii) the functional group $-X^bY^b$ in the compound of formula (Ib) is $-C(O)CH_2Cl$ and R^{*b} in the compound of formula (IIIb) is $-S-L^b-{}^nF$ wherein L^b is a C_{1-30} hydrocarbyl linker group optionally including 1 to 10 heteroatoms;and
^nF is a radioisotope of fluorine such as ^{18}F;

with a compound of formula (IVb):

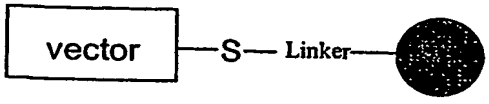
(IVb)

wherein R^4 is hydrogen or a thiol protecting group;

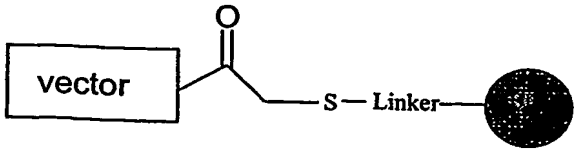
such that the compounds of formulae (IVb) and (Ib) may form a covalent bond to each other;

(b) separation of purified radiolabelled product of formula (IIIb) in the solution phase.

The compounds of formula (IVb) and (Ib) react to form the corresponding compound of formula (Vbi or Vbii):



(Vbi)



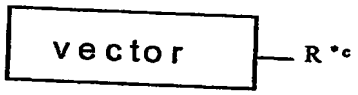
(Vbii)

The purification process using a compound of formula (IVb) may be performed at a non-extreme temperature such as 10 to 120°C, suitably at ambient temperature to 80°C and using an inert solvent such as xylene, N,N-dimethylformamide (DMF), DMSO, acetonitrile or chloroform. Preferably the solvent is an aqueous buffer or a mixture of acetonitrile and water or alcohol and water.

In a further aspect of the invention, there is provided a process comprising the steps of:

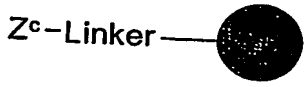
(a) contacting a solution-phase mixture of a radiolabelled product of formula (IIIc) and excess precursor of formula (Ic):

(Ic)



(IIIc)

wherein the functional group $-X^{\circ}Y^{c}$ in the compound of formula (Ic) is an aldehyde or ketone and R^{*c} in the compound of formula (IIIc) is =N-W-Linker-F where W is C_{1-15} alkyl or C_{7-15} aryl, with a compound of formula (IVc):



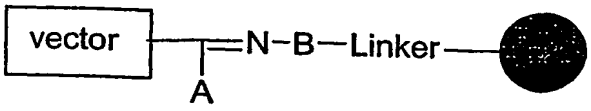
(IVc)

wherein Z^{c} is selected from $-NH_2$, hydrazine, hydrazide, aminooxy, phenylhydrazines, semicarbazide, or thiosemicarbazide;

such that the compounds of formulae (IVc) and (Ic) may form a covalent bond to each other; and

(b) separation of purified radiolabelled product of formula (IIIc) in the solution phase.

The compounds of formula (IVc) and (Ic) react to form the corresponding compound of formula (Vc):



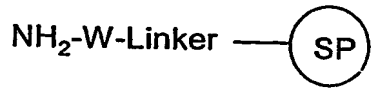
(Vc)

wherein A is hydrogen, C_{1-6}alkyl or aryl (such as phenyl) and B is –CO-NH-, -NH-, -O-, -NHCONH-, or –NHCSNH-.

In this aspect of the invention, compounds of the formula (IIc) have the formula NH_2-W-Linker-F where W is as described previously and F is preferably ^{18}F and the compound of formula (IIIc) is suitably a ^{18}F-labelled compound such as a peptide or drug substance and the precursor of formula (Ic) is the corresponding aldehyde or ketone.

The purification process using a compound of formula (IVc) may be performed at a non-extreme temperature such as 10 to 120°C, suitably at ambient temperature to 80°C and using an inert solvent such as xylene, N,N-dimethylformamide (DMF), DMSO, acetonitrile or chloroform. Preferably the solvent is an aqueous buffer or a mixture of acetonitrile: water or alcohol and water.

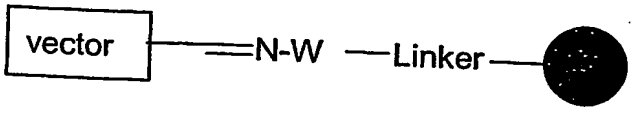
In a further embodiment of this aspect of the invention, the functional group $-X^cY^c$ in the compound of formula (Ic) is $-OSO_2R^3$ wherein R^3 is C_{1-15} alkyl or C_{1-10} alkylaryl and R^3 is optionally substituted by halo (preferably fluoro), for example R^3 is methyl, para-toluene, trifluoromethyl; and the purification is effected using a compound of formula (IVci) :



(IVci)

where W is selected from C_{1-15} alkyl or C_{7-15} aryl, -NH-, -NH-CO- or –O- and the linker is as described previously such that compounds of formula (Ic) and (IVci) form a covalent bond to each other.

The compounds of formula (IVci) and (Ic) react to form the corresponding compound of formula (Vci):



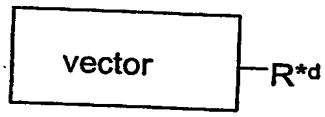
(Vci)

wherein W is as defined for the compound of formula (IVci).

In a further aspect of the invention, there is provided a process comprising the steps of:

(a) contacting a solution-phase mixture of a radiolabelled product of formula (IIId) and excess precursor of formula (Id):

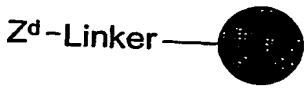
(Id)



(IIId)

wherein the functional group $-X^dY^d$ in the compound of formula (Id) is an amine, hydrazine, hydrazide , aminooxy, phenylhydrazine, or semicarbazide, thiosemicarbazide group and R^{*d} in the compound of formula (IIId) is =CH-Linker-F where the linker comprises an alkyl, aryl or polyethylene glycol component;

with a compound of formula (IVd):

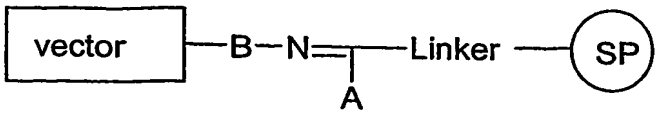


(IVd)

wherein Z^d is selected from aldehydes or ketone;
such that the compounds of formulae (IVd) and (Id) may form a covalent bond to each other; and

(b) separation of purified radiolabelled product of formula (IIId) in the solution phase.

The compounds of formula (Id) and (IVd) react to give compounds of formula (Vd):



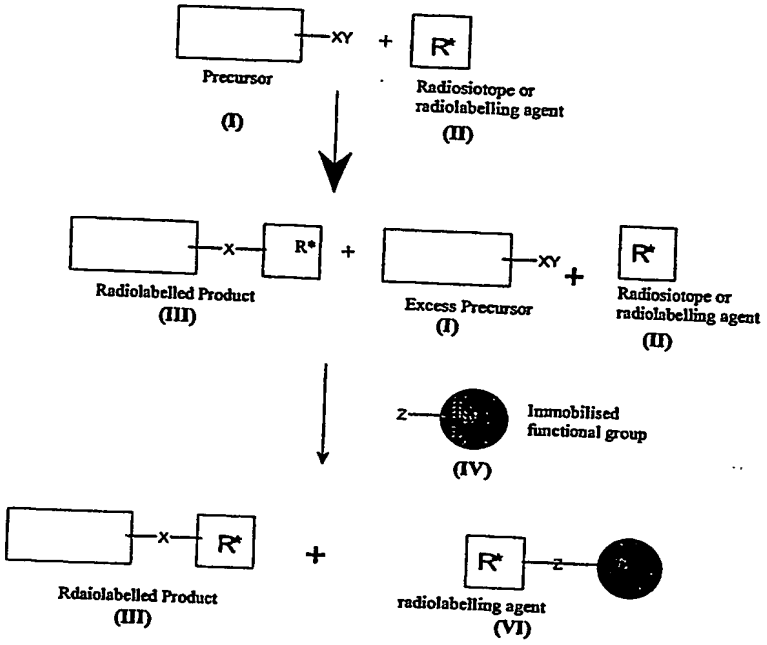
(Vd)

wherein A is hydrogen, C_{1-6}alkyl or aryl (such as phenyl) and B is –CO-NH-, -NH-, -O-, -NHCONH-, or –NHCSNH-.

The purification process using a compound of formula (IVd) may be performed at a non-extreme temperature such as 10 to 120°C, suitably at ambient temperature to 80°C and using an inert solvent such as xylene, N,N-dimethylformamide (DMF) , DMSO, acetonitrile or chloroform. Preferably the solvent is an aqueous buffer or a mixture of acetonitrile and water or alcohol and water.

In this aspect of the invention, the compound of formula (IIId) is suitably a ^{18}F-labelled compound such as a peptide or drug and the precursor of formula (Id) is suitably a modified peptide or drug carrying an aminooxy (NH_2-O-), hydrazide or hydrazine moiety.

In a further aspect of the invention, the compounds of formula (IV) may also be used to react covalently with any unreacted radiolabelling agent of formula (II) as shown in scheme 2 to give compounds of formula (VI). This purification process may be used instead of, or in addition to, processes described herein for removal of excess precursor.

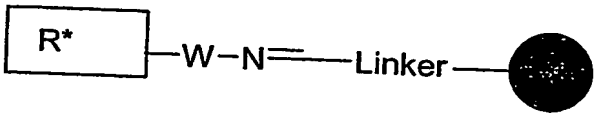


R* = radioisotope or radiolabelling agent
XY = functional groupY = leaving group
Z = scavenger group, selective for XY

Scheme II

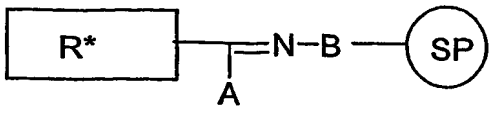
Thus, for example:

compounds of formula (IVd) may facilitate removal of unreacted radiolabelling agent of formula (IIc) from a reaction mixture resulting in a compound of formula (VId).



(IVd)

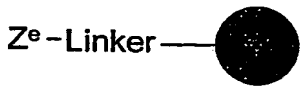
compounds of formula (IVc) may facilitate removal of unreacted radiolabeling agent having an aldehyde or ketone functionality resulting in a compound of formula (VIc).



(VIc)

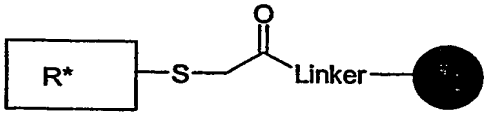
wherein A and B are as defined for the compound of formula (Vc).

In a further embodiment of this aspect of the invention, a compound of formula (IVe)



(IVe)

may be used wherein Z^e is Cl-CH_2-CO- or another haloacetyl containing moiety. Separation of unreacted radiolabelling agent containing a thiol moiety of formula (II) from a reaction mixture results in compound of formula (VIe).



(VIe)

The invention will now be illustrated by way of the following non-limiting examples.

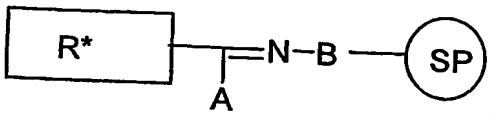
Examples

Example 1 Use of an isocyanate resin for purification of a ^{11}C-tracer

In both cases isocyanate resin was conditioned, using the same solvent as that from which precursor was to be extracted. Extraction efficiency was determined using HPLC . For studies using non-radioactive standard solutions, xylene was used as a control such that adjustments could be made for non-specific extraction and solvent loss.

Example 1(a) *In situ* resin conditioning and solid phase extraction (SPE) at elevated temperatures

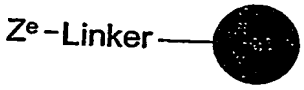
A cartridge (internal volume 0.067 ml) made of 3.2 mm (1/8") o.d. steel tubing and circular frits was charged with 25 mg of dry isocyanate functionalised



(VIc)

wherein A and B are as defined for the compound of formula (Vc).

In a further embodiment of this aspect of the invention, a compound of formula (IVe)



(IVe)

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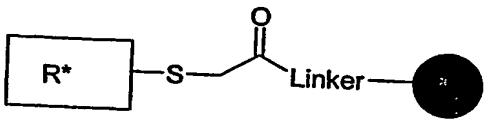

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polystyrene resin (Novabiochem). Solvent *ca* 5 ml (DCM, DMF or DMSO) was then passed through the cartridge and excess solvent removed with compressed air. For studies at elevated temperature a two-piece heater block, thermocouple and band heater were fitted around the cartridge and the entire assembly left *ca* 10 min to thermally equilibrate. 500 µl of solution containing precursor 2-Pyridin-4-yl-quinoline-8-carboxylic acid (2-methylamino-ethyl)-amide 0.5 mg and Xylene 1.3 mg were then passed through the cartridge using a syringe drive.

Example 1(b) SPE with external resin conditioning

For external conditioning 300 mg of isocyanate resin (Novabiochem) was suspended in excess solvent *ca* 9 ml for *ca* 5 min. The conditioned resin slurry was then loaded onto a 0.8 ml volume cartridge made of 6 mm (2/8") steel tubing. Excess solvent was removed with compressed air. Precursor solutions 300 µl or reaction mixture from automated preps 300 µl were passed through the cartridge using a syringe drive. A 1 ml syringe gave flow rates of 0.4 ml min^{-1}, equating to a contact time *ca* 2 min.

Example 1(c) SPE purification of [^{11}C-CH_3] 2-Pyridin-4-yl-quinoline-8-carboxylic acid (2-dimethylamino-ethyl)-amide reaction mixtures

Following [^{11}C]radiolabelling, 300µl of the resulting reaction mixture was drawn up from the reaction vial and dispensed (using a syringe drive) at a flow of 444µl min^{-1} through one of the conditioned isocyanate resin cartridges detailed in Examples 1(a) and 1(b). The cartridge was then flushed with 500µl of solvent and the combined solutions analysed be HPLC.

Claims

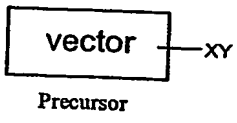
1. A process for purifying a radiolabelled product which comprises use of a solid-support bound scavenger group of formula (IV):

(IV)

wherein Z is a scavenger group and SP is a solid support.

2. A process comprising the steps of:

(a) contacting a solution-phase mixture of a radiolabelled product of formula (III) and excess precursor of formula (I):



Precursor

(I)

Radiolabelled Product

(III)

wherein XY is a functional group and R* is a radioisotope or radiolabelled portion; with a compound of formula (IV):

(IV)

wherein Z is a scavenger group;

such that the compounds of formulae (IV) and (I) may form a covalent bond to each other;

(b) separation of purified radiolabelled product of formula (III) in the solution phase.

3. A process according to claim 1 or 2 wherein the scavenger group Z is an

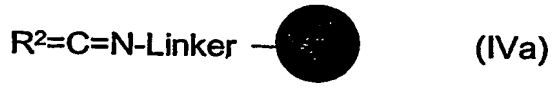
isocyanate, isothiocyanate, thiol, hydrazine, hydrazide, aminooxy, aldehyde or ketone.

4. A process according to any of claims 1 to 3 comprising the steps of:

(a) contacting a solution-phase mixture of a radiolabelled product of formula (IIIa) and excess precursor of formula (Ia):

wherein R^1 is C_{1-6} alkyl and R* is $[^{11}C]$-C_{1-4}alkyl, such as $-^{11}CH_3$

with a compound of formula (IVa):



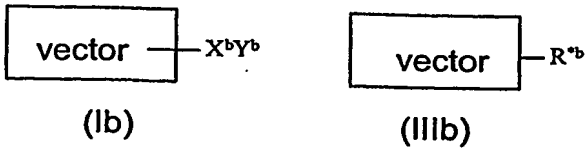
wherein R^2 is oxygen or sulphur

such that the compounds of formulae (IVa) and (Ia) may form a covalent bond to each other; and

(b) separation of purified radiolabelled product of formula (IIIa) in the solution phase.

5. A process according to any of claims 1 to 3 comprising the steps of:

(a) contacting a solution-phase mixture of a radiolabelled product of formula (IIIb) and excess precursor of formula (Ib):



wherein either

(i) the functional group $-X^bY^b$ in the compound of formula (Ib) is $-OSO_2R^3$ wherein R^3 is C_{1-15} alkyl or C_{1-10} alkylaryl and R^3 is optionally substituted by halo (preferably

fluoro), for example R^3 is methyl, para-toluene, trifluoromethyl, and R^{*b} in the compound of formula (IIIb) is a radiohalogen such as radiofluoro (for example ^{18}F) or radioiodo (such as ^{123}I, ^{124}I, or ^{125}I); or

(ii) the functional group $-X^bY^b$ in the compound of formula (Ib) is $-C(O)CH_2Cl$ and R^{*b} in the compound of formula (IIIb) is $-S-L^b-{}^nF$ wherein L^b is a C_{1-30} hydrocarbyl linker group optionally including 1 to 10 heteroatoms;and
^nF is a radioisotope of fluorine such as ^{18}F;

with a compound of formula (IVb):

(IVb)

wherein R^4 is hydrogen or a thiol protecting group;

such that the compounds of formulae (IVb) and (Ib) may form a covalent bond to each other;

(b) separation of purified radiolabelled product of formula (IIIb) in the solution phase.

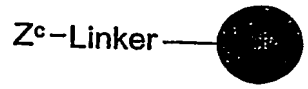
6. A process according to any of claims 1 to 3 comprising the steps of:
(a) contacting a solution-phase mixture of a radiolabelled product of formula (IIIc) and excess precursor of formula (Ic):

(Ic)

(IIIc)

wherein the functional group $-X^cY^c$ in the compound of formula (Ic) is an aldehyde

or ketone and R^{*c} in the compound of formula (IIIc) is =N-W-Linker-F where W is C_{1-15} alkyl or C_{7-15} aryl, with a compound of formula (IVc):

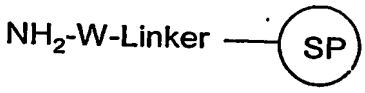


(IVc)

wherein Z^c is selected from $-NH_2$, hydrazine, hydrazide, aminooxy, phenylhydrazines, semicarbazide, or thiosemicarbazide;
such that the compounds of formulae (IVc) and (Ic) may form a covalent bond to each other; and

(b) separation of purified radiolabelled product of formula (IIIc) in the solution phase.

7. A process according to claim 6 wherein the functional group $-X^cY^c$ in the compound of formula (Ic) is $-OSO_2R^3$ wherein R^3 is C_{1-15} alkyl or C_{1-10} alkylaryl and R^3 is optionally substituted by halo (preferably fluoro), for example R^3 is methyl, para-toluene, trifluoromethyl; and the purification is effected using a compound of formula (IVci) :



(IVci)

where W is selected from C_{1-15} alkyl or C_{7-15} aryl, -NH-, -NH-CO- or –O- .

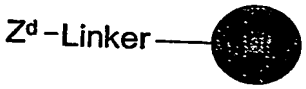
8. A process according to any of claims 1 to 3 comprising the steps of:
(a) contacting a solution-phase mixture of a radiolabelled product of formula (IIId) and excess precursor of formula (Id):

(Id)

(IIId)

wherein the functional group $-X^dY^d$ in the compound of formula (Id) is an amine, hydrazine, hydrazide , aminooxy, phenylhydrazine, or semicarbazide, thiosemicarbazide group and R^{*d} in the compound of formula (IIId) is =CH-Linker-F where the linker comprises an alkyl, aryl or polyethylene glycol component;

with a compound of formula (IVd):



(IVd)

wherein Z^d is selected from aldehydes or ketone;
such that the compounds of formulae (IVd) and (Id) may form a covalent bond to each other; and

(b) separation of purified radiolabelled product of formula (IIId) in the solution phase.

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/GB05/001796

International filing date: 11 May 2005 (11.05.2005)

Document type: Certified copy of priority document

Document details: Country/Office: GB
Number: 0410448.5
Filing date: 11 May 2004 (11.05.2004)

Date of receipt at the International Bureau: 21 June 2005 (21.06.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

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